TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

This *is a reissue of U.S. Pat. No. 6,525,060, issued on Feb. 25, 2003, from U.S. patent application Ser. No. 09/508,195, which* is a 371 National Phase application of PCT/SE99/02256, filed Dec. 2, 1999. *This reissue also claims the benefit of priority of Swedish Patent Application No. 9901271, filed Apr. 9, 1999, and Swedish Patent Application No. 9804211, filed Dec. 4, 1998.*

FIELD OF THE INVENTION

The present invention provides new triazolo[4,5-d]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), Circulation 90, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIIa Investigators (1994) Circulation 90, pp. 1631-1637; Neuhaus K. L. et. al. (1994) Circulation 90, pp. 1638-1642).

It has been found that adenosine 5'-diphosphate (ADP) acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion

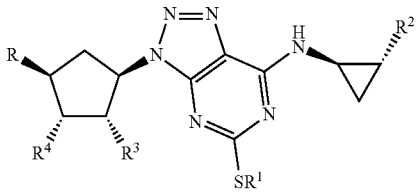
(see e.g. Antiplatelet Trialists' Collaboration (1994), Br. Med. J. 308, pp. 81-106 and Antiplatelet Trialists' Collaboration (1994), Br. Med. J. 308, pp. 159-168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow.

ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor which is as yet uncloned. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., Br. J. Pharmacology (1994), 113, 1057-1063, and Fagura et al., Br. J. Pharmacology (1998) 124, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see J. Med. Chem. (1999) 42, 213). Accordingly there is a need to find further P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

International Patent Application WO 9905143 discloses generically a series of triazolo[4,5-d]pyrimidine compounds having activity as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists. It has now been found that certain compounds within the scope of International Patent Application WO 9905143 but not specifically disclosed therein exhibit high potency combined with surprisingly high metabolic stability and bioavailibility, such that the predicted therapeutic dose for prolonged inhibition of aggregation in man shows advantage.

DESCRIPTION OF THE INVENTION

In a first aspect the invention therefore provides a compound of formula (I):



(I)

wherein:

R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is XOH, where X is CH_2, OCH_2CH_2 or a bond;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

provided that:

when X is CH_2 or a bond, R^1 is not propyl.

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

Alkyl groups, whether alone or as part of another group are straight chained and fully saturated.

Suitably R^1 is a C_{3-5} alkyl optionally substituted by one or more fluorine atoms. Preferably R^1 is C_{3-5} alkyl optionally substituted on the terminal carbon by three fluorine atoms. More preferably R^1 is 3,3,3,-trifluoropropyl, butyl or propyl.